

EYTHROPOIESIS-STIMULATING AGENTS IN PATIENTS
WITH HEMATOLOGIC MALIGNANCIES IN
NEWFOUNDLAND AND LABRADOR

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By

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Abstract

Anemia is common in cancer patients. Erythropoiesis-stimulating agents (ESAs) improve hemoglobin concentrations, decrease transfusion requirements and may improve quality of life. The American Society of Hematology (ASH) and the American Society of Clinical Oncology (ASCO) published guidelines for their use in 2002. The first objective was to estimate the number of patients with hematologic malignancies in Newfoundland and Labrador, who meet these criteria, that actually receive an ESA. The second objective was to determine whether there are demographic factors associated with receiving an ESA. The third objective was to review the literature around ESA use, tumor progression and survival. A review of the medical charts of 110 patients meeting the ASH/ASCO guidelines was undertaken. Patients had an average hemoglobin of 89.1 g/L, spent 75% of the time with a hemoglobin under 100 g/L and received an average of one transfusion every three weeks. More patients living in urban areas received an ESA than in rural areas. ESAs are important in supportive cancer care and measures should be taken to meet national standards.

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List of Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
CHOIR	Correction of Hemoglobin and Outcomes in Renal Insufficiency
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisone
CI	Confidence Interval
DNA	Deoxyribonucleic acid
ESA	Erythropoiesis-stimulating agent
FACT	Functional Assessment of Cancer Therapy
FACT-An	Functional Assessment of Cancer Therapy –Anemia
FACT-F	Functional Assessment of Cancer Therapy –Fatigue
FACT-G	Functional Assessment of Cancer Therapy –General
FDA	Food and Drug Administration
HIC	Human Investigation Committee
HR	Hazard Ratio
LASA	Linear analog scale assessment
NNH	Numbers needed to harm
ODAC	Oncology Drugs Advisory Committee
RPAC	Research Proposals Approvals Committee
RR	Relative Risk

SD	Standard Deviation
TEC	Technology Evaluation Center
TRALI	Transfusion-related acute lung injury

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- Appendix A Summary of ASCO/ASH Guidelines on the Use of Epoetin in Cancer Patients
- Appendix B Human Investigation Committee Approval
- Appendix C Research Proposals Approvals Committee Approval

Chapter 1: Introduction

1.1. Background

Anemia in patients with cancer has multiple etiologies, the most common of which are chemotherapy-related and cytokine-mediated anemia of chronic disease. Cancer-related anemia is very common in patients with hematologic malignancies and causes significant physical morbidity and impaired quality of life.¹ Cancer patients with anemia have significant fatigue, decreased physical and functional well-being and decreased ability to work.^{2,3}

While allogeneic red blood cell transfusions have traditionally been the mainstay of treatment for cancer-related anemia, they are associated with a variety of reactions, which range from mild allergic-type to severe reactions, like acute hemolytic transfusion reactions and transfusion-related acute lung injury (TRALI).⁴ Transfusions also have an associated risk of infectious disease transmission. While the risk of serious reactions and infectious disease transmission is low, when they occur they can be associated with significant morbidity and mortality.

Erythropoiesis-stimulating agents (ESAs), initially approved for the treatment of anemia associated with chronic kidney disease, have been demonstrated to improve hemoglobin concentrations or hematocrit levels⁵ and reduce transfusion requirements⁶ in patients with cancer-related anemia. There is some evidence that they improve quality of life in this population.⁷

Some safety concerns around the use of ESAs exist. They are known to increase the risk of thromboembolic disease⁸ and some recent data has suggested that they may adversely affect disease outcomes and mortality, particularly in patients not receiving chemotherapy.⁹ In many of these trials, however, the patients were not anemic¹⁰ and ESA doses were titrated to achieve hemoglobin concentrations higher than that recommended in published guidelines.^{11, 12} As well, many of the studies of ESAs in cancer patients have not been powered to detect survival differences.⁸ More well-powered, high-quality studies are needed to clarify this issue.

1.2. Study Purpose

Between 2001 and 2004, a variety of organizations^{11, 13, 14} developed evidenced-based clinical practice guidelines for ESA use in patients with cancer-related anemia. It has been the experience of the hematologists and medical oncologists in the province of Newfoundland and Labrador that the majority of patients meeting these guideline criteria do not receive an ESA.

The objectives of this study were two-fold. The first objective was to estimate the number of cancer patients in this province who meet guideline criteria, but yet fail to receive an ESA. Further to this, we sought to determine whether there are demographic factors associated with receiving an ESA. The second objective was to review the evidence around ESAs and their effect on tumor outcome and survival.

In order to achieve these objectives, a retrospective review of 110 patients' medical records was undertaken. All patients with hematologic malignancies meeting the

2002 American Society of Clinical Oncology (ASCO)/American Society of Hematology (ASH) guidelines¹¹ for receipt of an ESA during the period from January 2003 to December 2005 were included.

1.3. Outline

The first section of Chapter 2, the Literature Review, will begin with a review of the etiologies, prevalence and sequelae of cancer-related anemia. The next section will discuss the evidence for and safety concerns around the use of ESAs. Finally, a brief regulatory history of ESAs will be provided.

Chapter 3, the Methods, will detail the study design, patient selection criteria and data collection and analysis. In Chapter 4 the results obtained from the chart review examining local ESA utilization will be presented and Chapter 5 will provide a literature review examining tumor progression and survival data from randomized controlled trials.

Chapter 6, the Discussion, will review the implications of the results, the benefits and risks of ESAs, the study limitations and future directions. Finally, the study conclusions will be presented in Chapter 7.

Chapter 2: Review of Literature

2.1. Anemia in Patients with Cancer

Anemia, a deficiency in the concentration of hemoglobin-containing red blood cells, is a common problem in patients with cancer. There are several causes of cancer-related anemia, including direct tumor infiltration of the bone marrow, blood loss, myelosuppression from radiation and cytotoxic chemotherapeutic agents and anemia of chronic disease. The latter of these, anemia of chronic disease, is one of the most common reasons for anemia in patients with malignancies and is characterized by activation of macrophages and a variety of cytokines, including Interferon-g, Interferon-1 and tumor necrosis factor. These result in erythroid hypoplasia in the bone marrow, decreased red blood cell survival, disordered bone marrow utilization of iron and relatively low serum erythropoietin levels.¹⁵⁻¹⁸

The frequency of cancer-related anemia varies with the type of neoplasia and is very common in the hematologic malignancies. At diagnosis, 30 to 40% of patients with Hodgkin's lymphoma or non-Hodgkin's lymphoma⁸ and 70% of patients with multiple myeloma¹⁹ are anemic. The prevalence of anemia is even higher in the myelodysplastic

syndromes.²⁰ The following is the anemia classification scheme used by National Cancer Institute in the United States:²¹

Grade 0, within normal limits (hemoglobin 120 to 160 g/L for women, 140 to 180 g/L for men)

Grade 1, mild (hemoglobin 100 g/L to normal limits)

Grade 2, moderate (hemoglobin 80 to 99 g/L)

Grade 3, serious or severe (hemoglobin 65 to 79 g/L)

Grade 4, life threatening (hemoglobin less than 65 g/L)

Using this grading scheme, 74% of patients with non-Hodgkin's lymphoma have grade 3 anemia while receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).²²

The effects of anemia vary widely depending on a number of factors, including the degree of anemia, the rapidity of onset and the presence or absence of comorbidities. Mild to moderate anemia may produce typical signs and symptoms like pallor, fatigue, shortness of breath, palpitations and tachycardia. More severe or chronic anemia, despite the body's attempt to counter-regulate, eventually affects nearly every body system; some of the effects include heart failure, pulmonary edema, depression and cognitive dysfunction.¹

In addition to physical symptoms, anemia and the symptoms thereof, have been demonstrated to adversely affect quality of life in patients with cancer. Studies by Cella^{2,3} used validated subscales of the Functional Assessment of Cancer Therapy (FACT) questionnaire, the FACT-Anemia (FACT-An) and FACT-Fatigue (FACT-F) to assess outcomes in cancer-related anemia. In these studies, patients with hemoglobin levels less

than 120 g/L reported significantly more fatigue, more non-fatigue anemia-related symptoms, poorer physical well-being, poorer functional well-being, decreased ability to work (beyond that related to fatigue) and poorer overall quality of life.

There was some earlier evidence that anemia, and consequent tissue hypoxia, might reduce the efficacy of chemotherapy and radiation.²³ Additionally, severe anemia symptoms may necessitate reduced dosing or delays in the delivery of chemotherapy. These observations led to the hypothesis that cancer-related anemia may adversely affect disease control or survival. Recent clinical trials have not supported this hypothesis.^{9, 10}

Historically, allogeneic red blood cell transfusions have been the mainstay of treatment for severe anemia, while mild to moderate anemia was left untreated. While chronic anemia adversely affects multiple organ systems and quality of life, as described above, red blood cell transfusions are associated with a number of risks. Frequent transfusions are inconvenient for patients and place them at risk for transfusion reactions and infections. Most reactions, including febrile non-hemolytic transfusion reactions and minor allergic reactions, are mild. Approximately 800,000 units of red blood cells are transfused in Canada each year and the estimated numbers of serious adverse events for red blood cell transfusions are shown in Table 1.1.⁴ Included in the lung injury category is transfusion-related acute lung injury (TRALI). TRALI is a syndrome characterized by the acute onset of noncardiogenic pulmonary edema following transfusion. It is associated with high morbidity with the majority of patients requiring ventilatory support. Due to better donor selection and screening, the infectious risks associated with transfusions have decreased substantially and TRALI is now the most common serious adverse event associated with red blood cell transfusions.²⁴ The exact incidence is

unknown and estimates in the literature vary widely from 1 in 1,120 to 1 in 557,000 red blood cell units transfused.⁴ In addition to these risks, the blood supply represents a limited resource, which must be judiciously utilized.

Table 2.1. Approximate Number of Serious Adverse Events Associated with Red Blood Cell Transfusions in Canada Each Year

Adverse Event	Number per 800,000 Transfusions
Lung Injury	160
ABO Incompatible	20
Bacterial Sepsis	8
Hepatitis B Virus	4
Hepatitis C Virus	0.3
Human Immunodeficiency Virus	0.2

2.2. Use of Erythropoiesis-Stimulating Agents in Cancer-Related Anemia

Human erythropoietin is a heavily glycosylated peptide hormone with 165 amino acids and a molecular weight of 34 kDa. Approximately 90% of the body's erythropoietin is produced in the peritubular interstitial cells of the kidney and 10% is produced elsewhere, including the liver. Erythropoietin is not stored and the stimulus for its production is decreased oxygen tension in the tissues. Erythropoietin stimulates erythropoiesis by increasing the number of committed progenitor cells.

Epoetin alfa (Eprex, Epogen, Procret) is a recombinant glycoprotein with an amino acid sequence identical to that of natural human erythropoietin²⁵. The United States Food and Drug Administration (FDA) first approved Epoetin alfa (Procrit®, Ortho Biotech, Bridgewater, NJ; Epogen®, Amgen; Eprex®, Janssen-Cilag Ltd, High Wycombe, U.K.) as a pharmaceutical in 1989 for anemia associated with chronic renal failure. Since that time there have been numerous studies into its potential use in the management of cancer-related anemia.

Presently, there are two other erythropoiesis-stimulating agents (ESAs) available: darbepoetin alfa (Aranesp®, Amgen, Thousand Oaks, CA) and epoetin beta (NeoRecormon®, Roche, Basel, Switzerland). Epoetin alfa and beta have the same amino acid sequence, but differ in their glycosylation patterns. Darbepoetin alfa differs from epoetin alfa and beta in its amino acid sequence and glycosylation pattern. These agents belong to the same pharmacologic class and are treated equivalently with respect to efficacy and safety by the ASH/ASCO committee for the clinical practice guideline update on the use of epoetin and darbepoetin¹² and the FDA.

Important considerations for the use of ESAs in the treatment of cancer-related anemia include their hematologic response, effect on transfusion requirements, effect on quality of life, safety profile and effect on disease outcomes and survival. The remainder of this section will discuss each of these issues separately.

2.2.1. Erythropoiesis-Stimulating Agents and Hematologic Outcomes

Numerous clinical trials have examined the effect that ESAs have on hemoglobin concentration or hematocrit in patients with cancer. A multicenter double-blind placebo-controlled trial involving patients with hematologic and solid malignancies with hemoglobin concentrations less than 105 g/L randomized patients to receive recombinant human erythropoietin or placebo.⁵ Hematologic response was measured in three ways: 1) A rise in hematocrit level to 38% unrelated to transfusion, 2) An increase in hematocrit by at least 6% unrelated to transfusion, and 3) A change from baseline to final hematocrit. Using each of these measures, the group that received erythropoietin had a significant improvement in their hematocrit ($p = 0.0001$).

In another study involving anemic cancer patients receiving cisplatin-based chemotherapy, the mean hematocrit increased by 6% over the three-month study period in patients who received recombinant erythropoietin²⁶. This was significantly greater than the 1.3% rise in hematocrit seen in the group that received placebo.

In a recent review by the Cochrane Collaboration involving 22 trials and 4307 participants, the relative risk (RR) of a hematologic response was 3.46 (95% confidence interval, CI 3.09 to 3.87).⁸ These results confirm that use of ESAs in anemic cancer patients does result in increased hemoglobin or hematocrit.

2.2.2. Erythropoiesis-Stimulating Agents and Transfusion Requirements

Prior to ESAs, allogeneic red blood cell transfusion was the mainstay of treatment for anemia. Transfusions are associated with a number of risks, ranging from minor febrile and allergic reactions to significant and life-threatening reactions like TRALI. While improved donor selection and screening have reduced the risk of infectious disease transmission, there exists a small, but finite risk. Finally, frequent transfusions are inconvenient for patients and place strain on a limited resource.

There is good evidence that ESAs decrease transfusion requirements in patients with cancer-related anemia. For example, in a randomized, double-blind placebo-controlled trial by Cascinu et al., patients undergoing chemotherapy with hemoglobin levels less than 90 g/L were randomized to receive either recombinant human erythropoietin or saline. Over the course of the nine-week study period, 20% of patients in the erythropoietin arm required red cell transfusions versus 56% of patients in the placebo arm ($p = 0.01$).²⁷

In a large cohort study involving patients with a variety of hematologic and solid malignancies in 34 centers across Canada, transfusion requirements decreased when patients were treated with epoetin alfa.⁶ In the cohort that was not receiving chemotherapy, 29% had received at least one red cell transfusion in the month before study initiation. After two months of epoetin alfa therapy, there was a significant decrease in the percentage of patients who required transfusion (19%; $p < 0.02$). After four months of therapy, only 8% required transfusion ($p < 0.001$). The results were similar in the cohort that was undergoing chemotherapy. The number of patients

requiring transfusion in that group decreased from 34% in the month prior to the study, to 19% after two months on epoetin alfa therapy ($p < 0.001$), to 9% after four months of therapy ($p < 0.0001$).

In 1997, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) submitted a proposal to the Agency for Healthcare Research and Quality (AHRQ) for a review of the use of recombinant erythropoietin in cancer patients. This proposal was accepted and the task was awarded to the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC). The meta-analysis conducted by the TEC used randomized controlled trials that used subcutaneous epoetin alfa. This review, published in 2001, revealed a cumulative odds ratio of 0.38 (95% CI 0.28 to 0.51), suggesting that the use of epoetin alfa reduces the relative odds of receiving a red blood cell transfusion by 62%.²⁸

The issue of transfusion requirements was reviewed by the Cochrane Collaboration.⁸ This meta-analysis involving 42 trials and 6510 patients found that the relative risk of receiving a red blood cell transfusion was reduced by 36% in study groups that received ESAs (RR 0.64, 95% CI 0.60 to 0.68). It is now well accepted that in patients with cancer-related anemia, ESAs decrease transfusion requirements.

2.2.3. Effect of Erythropoiesis-Stimulating Agents on Quality of Life in Cancer Patients

Anemia in cancer patients is associated with fatigue, poor physical and functional well being, decreased ability to work and poor overall quality of life.^{2,3} ESAs have been shown to improve quality of life in patients with cancer-related anemia.

In a large, non-randomized multicenter Canadian trial with anemic cancer patients, two quality of life measurement tools were utilized: the 100-mm linear analog scale assessment (LASA) and the FACT-An questionnaires.⁶ The LASA tool assessed three aspects of quality of life: energy level, daily activities and overall well-being. The baseline scores were indicative of poor quality of life on all three aspects. By the end of the 16-week study, all scores in the group receiving recombinant erythropoietin had increased significantly ($p < 0.001$). Interestingly, there was a difference in the mean LASA change between patients who had a hematologic response to erythropoietin and those who did not. There was a significant positive correlation between change in LASA and change in hemoglobin on all three measures: energy level ($r = 0.30$, $p = 0.001$), daily activities ($r = 0.29$, $p = 0.002$) and overall well-being ($r = 0.25$, $p = 0.009$). The daily activities and overall well-being scores actually decreased in patients who did not have a hematologic response to erythropoietin therapy. Scores on the FACT-An also significantly improved in patients receiving erythropoietin, but only in the group not receiving chemotherapy ($p < 0.002$). As with the LASA data, there was a marked difference in the end-of-study FACT-An scores between those who responded to erythropoietin therapy and those who did not. There was a significant positive

correlation between change in hemoglobin and change in FACT-An score ($r = 0.33$, $p < 0.001$).

More recent studies have focused on the benefit of early therapy with ESAs. A multicenter, randomized trial involving anemic patients starting chemotherapy for hematologic malignancies compared early versus late therapy with epoetin alfa.⁷ Patients with baseline hemoglobin concentrations of 100 to 120 g/L were randomized to receive epoetin alfa immediately or to wait and receive it only if their hemoglobin concentration fell below 90 g/L. Patients who received epoetin alfa early had significantly higher FACT-General (FACT-G), FACT-An and FACT-F scores, as well as higher scores on the physical and functional well-being subscales. The group randomized to early epoetin alfa therapy also had higher energy level, daily activity and important activity LASA scores, and had fewer bed-rest and restricted activity days. Importantly, clinically relevant thromboembolic events were more common in the group that received early therapy (11.1% and 3.0% in the early and late groups, respectively, $p = 0.015$).

While there have been many studies looking at the question of whether quality of life in anemic cancer patients is improved with ESA therapy, the trials and methods of analysis used have been generally of lower quality. This question has not been definitively answered in a randomized controlled trial. In a recent review of this literature,⁸ Bohlius states, "Taking the results together, the results show an overall positive effect on health-related quality of life from Epo which seems unlikely to be due to chance."

2.2.4. Risks Associated With the Use of Erythropoiesis-Stimulating Agents

Recent concerns over the use of ESAs in patients with cancer have focused on two main aspects: 1) the risk of venous and arterial thromboembolic events, and 2) the effect on tumor outcomes and survival. The following examines the risk of thromboembolic events; new evidence around ESAs and tumor outcomes will follow in the subsequent section.

There is evidence that ESAs increase thromboembolic risk. In patients with chronic kidney disease, this was demonstrated in the CHOIR trial. In the CHOIR study,²⁹ 1432 patients with chronic kidney disease were randomized to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 135 g/L or a dose targeted to achieve a hemoglobin of 113 g/L. The primary end point was a composite of death, myocardial infarction, hospitalization for congestive heart failure and stroke. Significantly more events occurred in the high-hemoglobin group (125) than in the low-hemoglobin group (97; hazard ratio, HR 1.34, 95% CI 1.03 to 1.74, p = 0.03)

The Cochrane Collaboration reviewed the question of thromboembolic risk in cancer patients treated with ESAs in a meta-analysis.⁸ In this analysis involving 35 trials and 6769 participants, the risk of thromboembolic events was increased in patients treated with ESAs by 67% (RR 1.67, 95% CI 1.35 to 2.06). Of these trials, 21 included patients with solid malignancies only, 7 included only patients with hematologic malignancies and 7 studies included both solid and hematologic. Trials involved study patients who were and were not receiving cancer chemotherapy. Importantly, the risk of thrombosis varies with baseline risk. The Cochrane review addresses this issue by

calculating the numbers needed to harm (NNH) for several hypothetical baseline risks:

We calculated numbers needed to harm for several hypothetical baseline risks. In a population with an underlying risk of 2% the NNH would be 74.63 (95% CI 47.17 to 142.86), thus one thromboembolic complication would occur for every 75 patients treated. In a population with an underlying risk of 5% the NNH would be 29.87 (95% CI 18.87 to 57.14), thus for every 30 patients treated with Epo/Darbepo one additional thromboembolic complication might happen. In a population with a hypothetical baseline risk of 10% the NNH would be 14.93 (95% CI 9.43 to 28.57), thus for every 15 patients treated one additional thromboembolic complication may happen. These results show that the potential harmfulness of Epo/Darbepo depends on the underlying risk for thromboembolic complications.

2.2.5. Effect of Erythropoiesis-Stimulating Agents on Tumor Outcome and Survival

Recent evidence has suggested that in addition to increased thrombotic risk, ESAs may adversely affect tumor outcomes and survival. *In vitro* studies have demonstrated erythropoietin receptor expression in numerous tumor cell lines including breast, cervical, endometrial, papillary thyroid, non-small cell lung, squamous head and neck cancers and melanoma.³⁰ There is also evidence that endothelial cells have large numbers of erythropoietin receptors and that erythropoietin enhances their proliferation and migration.^{31, 32}

Several large clinical trials have recently demonstrated that ESAs may have a deleterious effect on survival in patients with cancer, including the BEST⁹ and EPO-CAN-20³³ trials. Other studies have demonstrated variable effects on disease control. Studies showing poorer tumor outcomes include ENHANCE¹⁰ and DAHANCA-10.³⁴ In both these trials, however, the majority of patients were not anemic. A recent meta-analysis examining the effect of ESAs on tumor outcomes and survival³⁵ found a significantly reduced risk of rapidly progressive disease for patients treated with epoetin beta (RR 0.78, 95% CI: 0.62, 0.99; P = 0.042).

Unlike the circumstance in which cancer patients are undergoing chemotherapy, there is reasonable evidence to suggest that ESAs not be used in cancer patients who are not undergoing chemotherapy. There is evidence for their use in patients with myelodysplasia^{36,37} but not in patients with other malignancies who are not undergoing chemotherapy. A large trial examining the issue of tumor outcome and survival in cancer patients not undergoing chemotherapy or radiation was the Danish Head and Neck Cancer Group (DAHANCA) 10 study.³⁴ This study revealed a higher mortality in patients treated with darbepoetin alfa. The results of the DAHANCA trial led to an FDA alert in February 2007 that raised concerns about the potential adverse effects of ESAs in anemic cancer patients who are not receiving chemotherapy. A subsequent trial in patients not undergoing chemotherapy³³ showed that survival was significantly lower in patients receiving epoetin alfa compared with the placebo. The largest of the trials to demonstrate reduced survival with ESAs in cancer patients not undergoing chemotherapy was Amgen Study 20010103.³⁸ The Clinical Study Report submitted to the FDA in March 2007 described a survival disadvantage in patients receiving darepoetin and led to

an added black box warning to epoetin alfa and darbepoetin in March 2007 stating that ESAs are not indicated for patients with cancer who are not receiving either chemotherapy or radiation. This stance is also held by the ASH/ASCO committee for the clinical practice update on the use of ESAs.

In summary, several randomized controlled trials have suggested an adverse effect on survival in cancer patients receiving ESAs. The evidence in this area is strong for patients who are not receiving chemotherapy but considerably weaker for patients who are. Specifically, many of these trials used ESAs in patients who were not anemic and their hemoglobins were raised to high targets. Additional well-designed randomized controlled trials in anemic cancer patients receiving chemotherapy are required to further elucidate their effects on tumor outcomes and survival in this patient population. These studies are reviewed in detail in Chapter 5.

The above discussion detailed the current state of the evidence for the benefits and risks of ESAs in patients with cancer-related anemia. In conclusion, there is substantial evidence that ESAs improve hemoglobin or hematocrit levels and decrease transfusions in anemic cancer patients. Anemia is associated with decreased quality of life in patients with cancer and it is likely that ESAs improve this. Additional well-designed studies are required to more definitively address this issue. ESAs do increase the risk of thromboembolic disease in several patient populations and the relative increase is related to underlying risk of thromboembolic disease. Recent trials have suggested poorer tumor outcomes and survival in cancer patients treated with ESAs. Many of these trials suffer from methodological flaws and further studies are needed.

2.3. Regulatory History of Erythropoiesis-Stimulating Agents

The first ESA approved by the FDA, Epoetin alfa, was licensed on June 1, 1989 and was indicated for the treatment of anemia associated with chronic kidney disease, both for patients with end stage kidney disease and those not on dialysis. Subsequently it was approved for anemia associated with zidovudine therapy in patients with AIDS in 1991, cancer-related anemia in 1993 and for pre-surgical administration in order to reduce perioperative transfusion requirements in 1996.

Since that time, changes to the label have included: a warning regarding higher mortality in patients with chronic renal failure with treatment regimens intended to maintain a hemoglobin level of 120 to 140 g/L in 1996, information regarding effects on response rate, time to progression, and overall survival in solid tumors in May 2004 following the ODAC meeting, a new dosing regimen (40,000 U/kg weekly) for the treatment of anemia associated with cancer chemotherapy in June 2004 and new information regarding pure red cell aplasia in October 2005. In March 2007, a warning was added about the risk of poorer survival in cancer patients not undergoing chemotherapy.

Darbepoetin alfa was first licensed in September 2001 for the treatment of anemia associated with chronic kidney disease, including patients on and not on dialysis. The license was expanded in July 2002 to include chemotherapy-associated anemia in cancer patients. Changes to the label for darbepoetin alfa have included: a new dosing regimen (40,000 U/kg weekly) for the treatment of anemia associated with cancer chemotherapy in June 2004, information about the effects on thrombotic events and tumor promotion in

December 2004 and new information regarding pure red cell aplasia in October 2005. In March 2007 the warning about decreased survival in cancer patients not undergoing chemotherapy was added.

All of the ESAs currently licensed are considered to belong to the same pharmacologic class and are treated equivalently by the FDA with respect to safety issues. In November 2007, the warnings about ESAs in cancer patients were strengthened as a result of the newest studies showing more rapid tumor growth and shortening survival. In February 2008, the FDA approved a revised label for ESAs including the updated boxed warning stating that ESAs "shortened overall survival and/or time-to-tumor progression in clinical studies in patients with breast, non-small-cell lung, head and neck, lymphoid, and cervical cancers, when dosed to target hemoglobin of greater than or equal to 12 grams per d/l."

In summary, cancer-related anemia is multifactorial with the most common causes being chemotherapy-associated anemia and cytokine-mediated anemia of chronic disease. Anemia is very common in patients with hemologic and solid cancers and is associated with significant physical morbidity and decreased quality of life. Historically red blood cell transfusions were the mainstay of therapy for cancer-related anemia. Frequent transfusions have associated risks including a variety of transfusion-related reactions and infectious disease transmission. ESAs are a group of pharmaceuticals made with recombinant DNA technology that are identical or similar to human erythropoietin. ESAs have been shown to raise hemoglobin or hematocrit and decrease transfusion requirements in patients with cancer-related anemia. They may improve quality of life.

ESAs increase the risk of thromboembolic events and may adversely affect disease outcomes or survival, particularly in patients not undergoing chemotherapy. The FDA has recently strengthened its warnings about the use of ESAs in cancer patients. This is presently an area of very active research.

Chapter 3: Methods

3.1. Study Design

Guidelines from the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) regarding the use of ESAs in patients with cancer exist ¹¹. The first objective of this study was to determine the number of patients in Newfoundland and Labrador who meet guideline criteria to receive ESAs and actually do receive one. Associated with this objective, we sought to determine whether there were demographic factors associated with receipt of an ESA. The second objective was to review the randomized trial data on ESA use in patients with malignancies.

In order to accomplish the first objective a retrospective design was used in which data were obtained from patients' medical records. Ethical approval for the study was obtained through the Human Investigation Committee (HIC) at Memorial University, St. John's, Newfoundland and Labrador on February 16, 2006 (Appendix A). The Research Proposals Approvals Committee (RPAC) of Eastern Health approved the study on June 13, 2006 (Appendix B).

Patients with hematologic malignancies meeting ASCO/ASH criteria for receiving ESAs were selected for the study. Specifically, patients with diagnoses of multiple myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukemia undergoing chemotherapy with a hemoglobin concentration of less than 100 g/L were included. As well, in accordance with the guidelines, patients with myelodysplasia (not receiving chemotherapy) and hemoglobin concentrations less than 100 g/L were

included. As these guidelines were published in October 2002, it was assumed that several months would be required for these to translate into clinical practice. Hence, the period from which data were collected began in January 2003. The data collection period was three years long and ended in December 2005. Patients eligible for the study were identified according to the above criteria through the Medical Records Department at the Health Sciences Centre, St. John's. Data were collected from patients' electronic medical records on the MEDITECH system (Medical Information Technology, Inc., Westwood, MA) in August 2007.

3.2. Patient Selection

Patients were included in the study if they met the ASCO/ASH guidelines for receiving an ESA. Specifically, the inclusion criteria for the study required that patients had a diagnosis of multiple myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukemia and received chemotherapy, or had a diagnosis of myelodysplasia, during the period of January 1, 2003 to December 31, 2005. In accordance with ASCO/ASH guidelines for receipt of an ESA, patients had to be anemic with a hemoglobin concentration of 100 g/L or less. All male and female patients meeting the study criteria from all areas of Newfoundland and Labrador were included.

Patients were excluded if their hemoglobin concentration was very transiently below 100 g/L or if it was evident that their anemia was clearly secondary to another etiology, for example, gastrointestinal or postoperative bleeding. Data were collected on all eligible patients (110 in total).

3.3. Data Collection

Data were collected on all 110 patients meeting the study inclusion criteria. The same individual collected all data and the data extraction method was the same for all patients. Although the entire data collection period spanned three years, for an individual patient, the “study period” was defined as the period of time during which the patient met guideline criteria for receiving an ESA. For patients with multiple myeloma, non-Hodgkin’s lymphoma and chronic lymphocytic leukemia, the study period began at the start of chemotherapy. For patients with myelodysplasia, the study period began either when the diagnosis was made or at the beginning of the data collection period, January 1, 2003. An individual patient’s study period ended when one of the following occurred: 1) the chemotherapy regimen was finished and a one-month follow-up period during which the chemotherapy was likely to be contributing to the patient’s anemia was over, 2) the three-year data collection period ended, 3) the patient was lost to follow-up or 4) the patient died. Information obtained included the patients’ age, diagnosis, start and completion dates of chemotherapy, hemoglobin measurements obtained during the patients’ individual study periods as defined above, whether or not patients received an ESA during their study period, the number of red blood cell transfusions patients received during their study period and whether their place of residence was urban or rural (based on the patients’ postal codes). As it was collected, data were entered into an SPSS (SPSS Inc, Chicago, Il) data file.

3.4. Data Analysis

Data analysis was completed using SPSS statistical software. The number of patients receiving an ESA was calculated using the descriptive statistics function. In addition to the primary outcome, the patients' average hemoglobin concentrations and percentage of time spent with hemoglobin concentrations less than 100 g/L were calculated. Because patients were followed for variable durations of time and because hemoglobin concentrations were measured at variable intervals (for example, blood work may have been done daily if a patient was admitted during their study period versus prior to every cycle of outpatient chemotherapy), these measurements had to be standardized for the purpose of analysis. This was done by calculating an average weekly hemoglobin for each study week for each patient. If a patient had multiple hemoglobin measurements for a given week, then the average of these values was determined. If a period of time elapsed without a hemoglobin measurement, then a weekly value (or several weekly values, as necessary) was estimated by taking the mean of preceding and succeeding measurements. These values were then used to calculate the patients' average hemoglobin concentration over the total number of study weeks as well as the percentage of time spent with hemoglobin concentrations less than 100 g/L. The number of red blood cell transfusions received was also calculated.

The demographic features associated with receipt of an ESA were calculated using an independent samples t-test and chi-squared test to determine whether there was a relationship between the primary outcome and age and place of residence, respectively.

These were calculated using the descriptive statistics functions using SPSS. For these tests statistical significance was taken to be less than 0.05.

3.5. Literature Review

A search of PubMed and EMBASE was conducted by combining the following the MeSH terms: erythropoietin; erythropoietin, recombinant, darbepoetin, anemia and cancer. In addition, the 2007 ASH annual meeting abstracts, FDA reports and reference lists of clinical trials and systematic reviews were searched for relevant articles.

Randomized controlled trials were included in this review.

Chapter 4: Results

4.1. The Number of Patients Receiving an Erythropoiesis-Stimulating Agent

Patients with hematologic malignancies meeting the 2002 ASCO/ASH criteria for receiving an ESA during the study period were identified. A total of 110 patients met these criteria and their medical records were reviewed. Anemic patients (with hemoglobin concentrations less than 100 g/L) with diagnoses of multiple myeloma, non-Hodgkin's lymphoma or chronic lymphocytic leukemia undergoing chemotherapy and patients with myelodysplasia (not receiving chemotherapy) were included. The distribution of study patients with each of these diagnoses is shown in Figure 4.1.1.

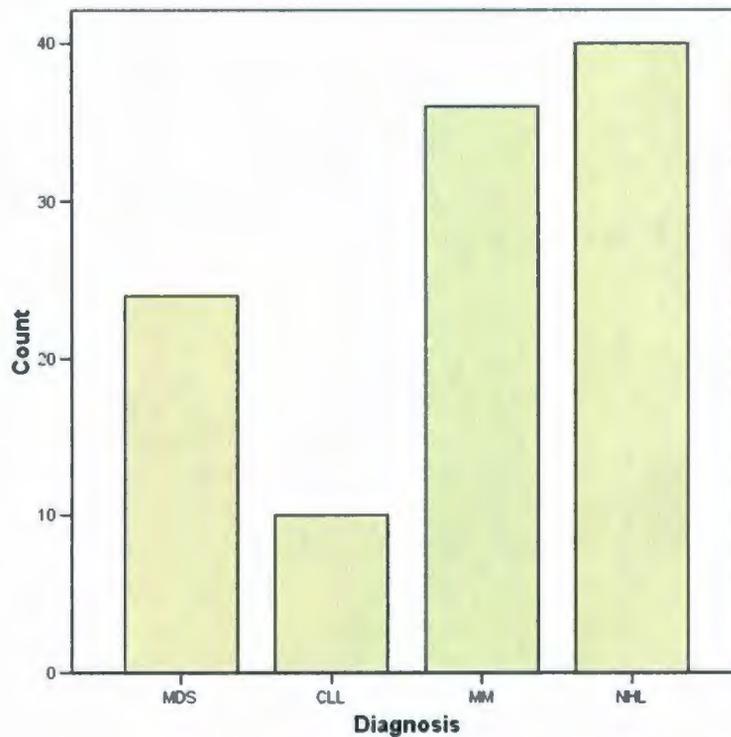


Figure 4.1.1. Distribution of Study Patients' Diagnoses

The primary goal of this study was to determine the number of patients in Newfoundland and Labrador meeting guideline criteria for receiving an ESA that actually do receive these drugs. For this population of 110 patients, only 16.4% actually received the ESA, epoetin alfa (Eprex). This result is shown in Figure 4.1.2.

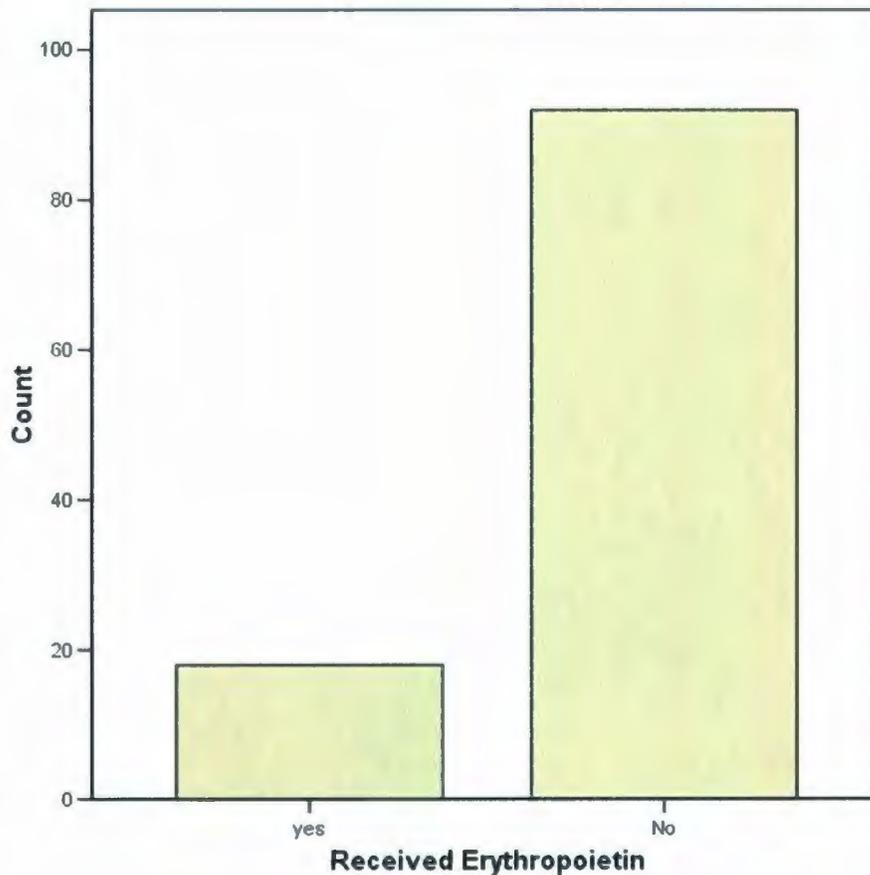


Figure 4.1.2. Proportion of Study Patients Receiving Erythropoietin

The extent of anemia in this patient sample was measured in three ways: 1) the overall mean weekly hemoglobin concentration, 2) the proportion of time that the study patients' hemoglobin was less than 100 g/L and 3) the number of red blood cell transfusions patients received.

The overall mean weekly hemoglobin concentration for this study population was 89.1 g/L (standard deviation, SD, 19.4 g/L). This result was calculated using the transformed average weekly hemoglobin concentration and the total number of study weeks (2376). Clearly, this average hemoglobin is much lower than the hemoglobin at which the current guidelines recommend the use of an ESA. The SPSS output file yielding this result, along with the median and mode hemoglobin concentrations and quartiles is shown in Table 4.1.1.

Table 4.1.1. Overall Mean Weekly Hemoglobin Concentration

Hb extrapolated		
N	Valid	2376
	Missing	0
Mean		89.1199
Median		88.0000
Mode		83.00
Std. Deviation		19.40664
Percentiles	25	78.0000
	50	88.0000
	75	99.0000

The second way in which the extent of anemia was measured was with the proportion of time the patients spent with a hemoglobin concentration that was less than 100 g/L. This result is shown in Table 4.1.2.

Table 4.1.2. Proportion of Time Hemoglobin Concentration was Less Than 100 g/L

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Not Selected	588	24.7	24.7	24.7
	Selected	1788	75.3	75.3	100.0
	Total	2376	100.0	100.0	

It can be seen from Table 4.1.2, that for 75.3% of the study weeks, the patients' hemoglobin concentrations were less than 100 g/L. This indicates that the patients spent three quarters of the study weeks with hemoglobin concentrations less than that required to receive an ESA according to guidelines.

The third way in which this study sought to characterize the extent of anemia in this study population was by determining the number of transfusions that patients received. In these 110 patients, 781 red blood cell transfusions were administered over the study weeks. With a total of 2376 study weeks, patients received an average of 0.33 transfusions per week, in other words approximately one transfusion every three weeks. There were an average of 7.1 transfusions per patient per study period.

In summary, the medical records of all 110 patients with diagnoses of multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia or myelodysplasia that met the ASCO/ASH 2002 guidelines for receiving an ESA were reviewed. The majority of these patients had non-Hodgkin's lymphoma; chronic lymphocytic leukemia was the most infrequent diagnosis. Of the 110 study patients, only 16.4% received an ESA during the study period. These patients had moderate anemia, as the overall mean weekly hemoglobin concentration was 89.1 g/L. For 75.3% of the study weeks, the

patients' hemoglobin concentrations were under 100 g/L. Patients were transfused an average of 7.1 times throughout their study period, with an average of one red cell transfusion every three weeks.

4.2. Erythropoiesis-Stimulating Agents and Demographic Factors

In this study, the effect of two demographic factors on receiving an ESA was examined: age and place of residence. An independent-samples t-test was conducted to determine whether there was any difference in the ages of the patients that received an ESA and those who did not. The SPSS output file for this test is shown in Table 4.2.1.

Table 4.2.1. Comparison of Patient Age in the Groups Receiving and Not Receiving an ESA

Group Statistics				
Did the pt receive epo?	N	Mean	Std. Deviation	Std. Error Mean
Age yes	18	72.94	11.409	2.699
No	92	70.12	10.428	1.087

Independent Samples Test										
		Levene's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
									Lower	Upper
Age	Equal variances assumed	.450	.504	1.035	108	.303	2.825	2.729	-2.584	8.234
	Equal variances not assumed			.974	22.897	.340	2.825	2.901	-3.177	8.827

As shown in Table 4.2.1, the mean age in the group receiving an ESA was 72.9 years (SD 11.4) versus 70.1 years (SD 10.4). There was no significant difference between the ages of the patients in these groups ($p = 0.3$). This is shown graphically in Figure 4.2.1.

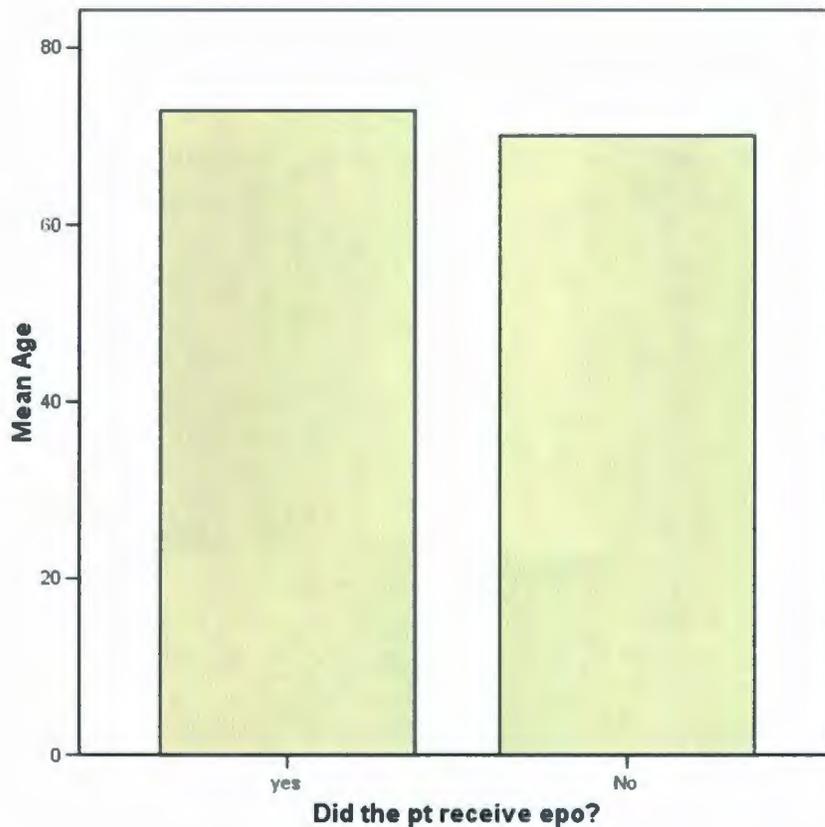


Figure 4.2.1. Patient Age in the Groups Receiving and Not Receiving ESA

The second demographic factor that was investigated was place of residence. A chi-squared test was performed to determine whether there was a difference in the number of patients receiving an ESA from urban and rural areas of the province. More

patients from urban areas (61.1%) than rural areas (38.9%) received an ESA ($\chi^2 = 3.997$, $p = 0.046$). The output file is shown in Table 4.2.2 and the corresponding graph in Figure 4.2.2.

Table 4.2.2. Comparison of Place of Residence in the Groups Receiving and Not Receiving an ESA

Residence.1 * Did the pt receive epo? Crosstabulation

		Did the pt receive epo?		Total	
		yes	No		
Residence.1	Urban	Count	11	33	44
		Expected Count	7.2	36.8	44.0
		% within Residence.1	25.0%	75.0%	100.0%
		% within Did the pt receive epo?	61.1%	35.9%	40.0%
		% of Total	10.0%	30.0%	40.0%
Rural	Count	7	59	66	
	Expected Count	10.8	55.2	66.0	
	% within Residence.1	10.6%	89.4%	100.0%	
	% within Did the pt receive epo?	38.9%	64.1%	60.0%	
	% of Total	6.4%	53.6%	60.0%	
Total	Count	18	92	110	
	Expected Count	18.0	92.0	110.0	
	% within Residence.1	16.4%	83.6%	100.0%	
	% within Did the pt receive epo?	100.0%	100.0%	100.0%	
	% of Total	16.4%	83.6%	100.0%	

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.997 ^a	1	.046		
Continuity Correction ^b	3.014	1	.083		
Likelihood Ratio	3.915	1	.048		
Fisher's Exact Test				.065	.042
N of Valid Cases	110				

a. Computed only for a 2x2 table

b. 0 cells (.0%) have expected count less than 5. The minimum expected count is 7.20.

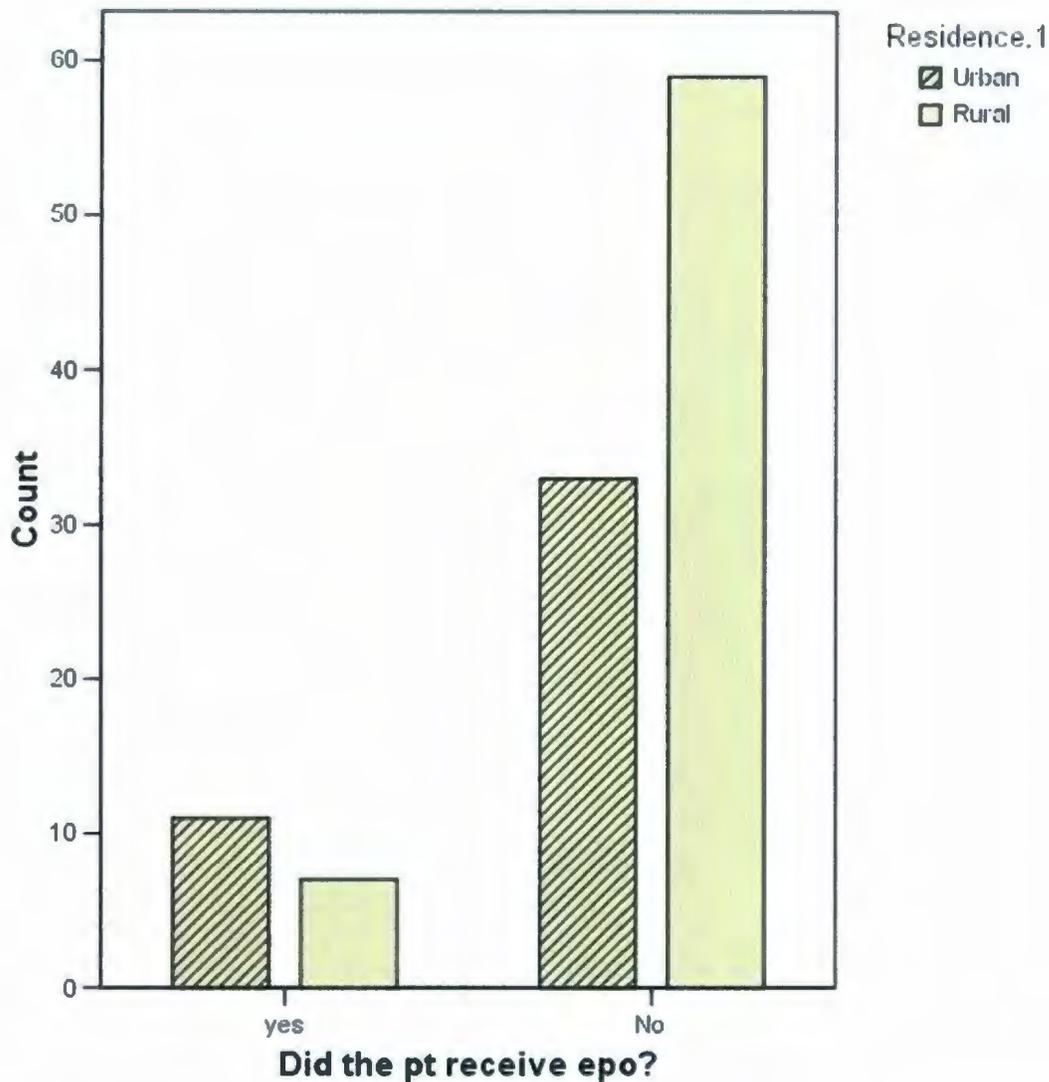


Figure 4.2.2. Place of Residence in the Patients Receiving and Not Receiving an ESA

The secondary objective of this study was to determine whether there were demographic factors associated with receipt of an ESA. Two demographic factors were considered: age and place of residence. It was determined that there was no difference between the age of the groups receiving and not receiving an ESA, however significantly more patients from urban areas of the province received an ESA than those from rural areas.

In summary, in this sample of patients meeting the ASCO/ASH criteria to receive an ESA in Newfoundland and Labrador, 16.4% of patients received one. The study patients had moderate anemia, with an average weekly hemoglobin of 89.1 g/L overall. For three quarters of the study period, the patients had hemoglobin concentrations of less than 100 g/L and they received an average of one red blood cell transfusion every three weeks. The average age was not different between the patients receiving and not receiving an ESA, however more patients from urban areas of the province received an ESA than those from rural areas.

Chapter 5: Effect of Erythropoiesis-Stimulating Agents on Tumor Outcome and Survival: A Literature Review

There is substantial evidence that ESAs improve hemoglobin concentrations, decrease transfusion requirements and likely improve quality of life in anemic cancer patients. However, recently there has been increasing attention to the safety of ESAs in this patient population. Numerous randomized controlled trials published in peer-reviewed journals have examined disease control and survival in patients receiving ESAs. There have also been some recent meta-analyses of these trials.⁸³⁵ The following is a review of the randomized trial data concerning tumor outcome and survival in anemic cancer patients receiving ESAs. Table 5.1 provides a summary of the trials included in this review.

A number of recent randomized controlled trials have demonstrated poorer tumor outcomes or survival in patients with cancer-associated anemia receiving ESAs. In the BEST trial,⁹ based in Montreal, 939 patients with metastatic breast cancer undergoing first-line chemotherapy were randomized to receive epoetin alfa 40,000 units weekly or placebo. In this study, erythropoietin was initiated when the hemoglobin fell below 130 g/L. The primary endpoint was 12-month overall survival. Recombinant erythropoietin administration was stopped early in accordance with a recommendation from the Independent Data Monitoring Committee because there was a higher mortality in the treatment group. At the end of the 12-month study period, overall survival was 70% in the epoetin alfa group and 76% in the placebo group ($p = 0.01$). There was no difference between tumor responses or time to disease progression between the two groups and the

reason for the survival difference could not be established. The ENHANCE trial was a multicenter double-blind randomized placebo-controlled trial in patients undergoing radiotherapy for head and neck cancer.¹⁰ This trial was designed to investigate whether anemia correction with epoetin beta could improve tumor outcome. In this study 351 patients were randomized to receive epoetin beta 300 units/kg three times weekly or placebo from days 10 to 14 before and continuing throughout radiotherapy. Locoregional progression-free survival was poorer in the epoetin beta group than in the placebo group (adjusted relative risk 1.62, 95% CI 1.22 to 2.14, $p = 0.0008$). The majority (82%) of patients treated with epoetin beta had hemoglobin concentrations greater than 140 g/L (women) or 150 g/L (men) compared with 15% treated with placebo. The results of the BEST and ENHANCE trials, along with study N93-004³⁹ (discussed below) were presented at the Oncology Drugs Advisory Committee (ODAC) meeting in 2004. The members of the ODAC agreed that the results of these trials raised concerns that required further study

In the EPO-CAN-20 trial³³, patients with advanced non-small cell lung cancer were given either epoetin alfa or placebo to achieve a hemoglobin concentration of 120 to 140 g/L. This study was terminated after only 70 patients had been randomized because of decreased survival in patients treated with epoetin alfa (median survival 63 versus 129 days; HR, 1.84; $P = .04$).

In addition to the randomized controlled trials published in peer-reviewed journals discussed above, several other studies have examined the effect of ESAs on tumor outcome and survival. Study N93-004³⁹ was a randomized controlled non-inferiority trial of 224 patients with small cell lung cancer undergoing treatment with chemotherapy and

radiation. Patients received either Epogen at 40,000 IU/kg weekly or placebo and Epogen was withheld if the hemoglobin increased above 160 g/L. The objective of this study was to exclude a 15% reduction in overall response rates. This study met its objective with an observed 6% difference in response rate between the two groups (95% CI -6% to 18%). No significant difference in overall survival was detected HR 1.17 (95% CI: 0.89, 1.55). Study 20000161⁴⁰ was a randomized, double-blind placebo-controlled study of Aranesp in anemic patients with lymphoproliferative malignancies. In this study, 344 patients undergoing chemotherapy were randomized to receive either Aranesp to achieve a target hemoglobin of 150 g/L (men) or 140 g/L (women) or placebo. Overall survival was shorter in the group who received Aranesp (HR 1.37; 95% CI 1.02, 1.83). The DAHANCA 10 study³⁴ was a randomized controlled trial of darbepoetin in patients undergoing radiotherapy for head and neck cancer. The interim analysis was made available online and showed poorer outcomes in the group treated with darbepoetin for the primary end point of locoregional failure.

With the exception of myelodysplasia,^{36,37} there is no evidence to support ESA use for the treatment of cancer-associated anemia in patients not undergoing chemotherapy. This is reflected in the ASH/ASCO guidelines.^{11,12} Amgen study 20010103⁴¹ was a randomized, double-blind trial of darbepoetin versus placebo in 989 patients with cancer not undergoing chemotherapy of myelosuppressive radiation. This trial showed that overall survival was poorer in the darbepoetin than in the control arm (HR 1.30; 95% CI 1.07 to 1.57; $p = 0.008$).

The question of survival was addressed in a 2006 Cochrane Review.⁸ A meta-analysis of 42 trials involving 8,167 patients was conducted; 25 trials included solid

tumors only, 8 studies included hematologic malignancies only, 8 studies included both solid and hematological malignancies and one study involved patients with MDS. In 29 studies, patients were undergoing chemotherapy, in 8 trials patients were undergoing radiotherapy or radiochemotherapy, and in two studies the treatment was categorized as unclear. Three studies involved patients not undergoing chemotherapy or radiation. In 20 studies, the average baseline hemoglobin was below 100 g/L, in 8 studies the average baseline hemoglobin was between 100 and 120 g/L, in 7 studies the baseline hemoglobin was above 120 g/L, and in 7 studies the hemoglobin at baseline was not reported. Results were taken from full text publications for 12 studies, unpublished data for 5 studies unpublished and abstracts for 3 studies. For 22 studies data were taken from FDA documents; of those, 8 were exclusively published in FDA documents. This meta-analysis revealed a hazard ratio of 1.08 (HR 1.08; 95% CI 0.99 to 1.18) in favor of placebo or no treatment over treatment with an ESA. There was little heterogeneity between the trials (chi-square = 44.04; df = 39; p = 0.27; I² = 11.5%) and funnel plot analysis did not suggest asymmetry (p = 0.35).

The same Cochrane Review⁸ analyzed 13 trials with data about tumor response. Nine trials included only solid tumors, 3 studies included only hematologic malignancies and 1 study included both solid and hematologic tumors. In 4 studies patients received either radiotherapy or radiochemotherapy and in 9 studies patients received chemotherapy. The average baseline hemoglobin was below 100 g/L in 5 studies, between 100 and 120 g/L in 4 studies, greater than 120 g/L in 3 studies and not reported in 1 study. This meta-analysis showed a relative risk of 1.12 (RR 1.12; 95% CI 1.01 to 1.23) in favor of erythropoietin. There was marked heterogeneity (chi-square = 25.84; df

= 14; $p = 0.03$; $I^2=45.8\%$) and funnel plot analysis suggested some asymmetry ($p = 0.03$). The majority of these trials were not adequately powered to detect a difference in tumor response and those that were, were available only in abstract form or in documents submitted to the FDA ODAC meeting. The conclusion was that the effect of ESAs on tumor response could not be reliably assessed based on the available data.

Another recent meta-analysis³⁵ included 9 randomized studies of epoetin beta or placebo. There were a total of 1413 patients, 56% of which had hematological and 44% of which had solid malignancies. The average baseline hemoglobin in these studies was 99 g/L and the average maximum hemoglobin during treatment was 126 g/L with epoetin beta and 116 g/L with control. Overall survival during the first six months was similar with epoetin beta and control (0.31 versus 0.32 deaths per patient-year). No increased mortality risk was seen with epoetin beta (RR 0.97; 95% CI 0.69 to 1.36; $p = 0.87$). There was a significantly reduced risk of rapidly progressive disease with epoetin beta (RR 0.78; 95% CI 0.62 to 0.99; $p = 0.042$).

In summary, it remains unclear whether ESAs affect tumor progression or survival in patients with cancer-related anemia. In the meta-analyses discussed above (both published in 2006) no significant differences in mortality were observed. The conclusion from the Cochrane Review⁸ was that the effect of ESAs on tumor response could not be adequately assessed given the quality of the available data. The Aapro et al³⁵ review found a reduced risk of rapidly progressive disease, however with only 9 studies, there was clearly missing data. Consistent problems with the majority of available data have been the high baseline hemoglobin concentrations and target hemoglobin concentrations greater than 120 g/L. Some of the trials reviewed above

included patients not undergoing chemotherapy. The effect of ESAs, titrated to maintain a hemoglobin concentration near 120 g/L, on a population of patients with cancer-related anemia undergoing chemotherapy is still unknown.

Table 5.1. Randomized Trials of Erythropoietin

Author, Year	Tumour Response	Overall Survival
Abels, 1993 ⁴²	x	
Bamias, 2003 ⁴³	x	x
Boogaerts, 2003 ⁴⁴		x
Cascinu, 1994 ²⁷	x	x
Case, 1993 ⁵		x
Cazzola, 1995 ⁴⁵	x	x
Chang, 2005 ⁴⁶		x
Dammacco, 2001 ⁴⁷	x	x
Deal Mastro, 1997 ⁴⁸		x
Dunphy 1999 ⁴⁹		x
EPOCAN-15 ⁵⁰		x
EPOCAN-20 ⁵¹		x
EPOGBR-7 ⁵²	x	x
GOG-0191 ⁵³		x
Hedenus, 2002 ⁵⁴		x
Hedenus, 2003 ¹⁰		x
Henke, 2003 ¹⁰		x
Henry, 1995 ²⁶		x
INT-1 ⁵⁵		x

INT-3 ⁵⁶		x
Kotasek, 2003 ⁵⁷		x
Kurz, 1997 ⁵⁸		x
Leyland- Jones, 2003 ⁹	x	x
Littlewood, 2001 ⁵⁹	x	
Machtay, 2004 ⁶⁰	x	x
N93 004 ⁶¹	x	x
O'Shaugnessy, 2005 ⁶²		x
Oberhoff, 1998 ⁶³		x
Osterborg, 1996 ⁶⁴		x
Osterborg, 2002 ⁶⁵	x	x
Overgaard ³⁴		x
P-174 ⁶⁶		x
Razzouk, 2004 ⁶⁷		x
Rose, 1994 ⁶⁸		x
Savonije, 2006 ⁶⁹		x
Smith, 2003 ⁷⁰		x
Ten Bokkel, 1998 ⁷¹	x	x
Thatcher, 1999 ⁷²		x
Thompson, 2000 ⁷³		x
Throuvalas, 2000 ⁷⁴	x	x
Vadhan- Raj, 2004 ⁷⁵	x	x
Vansteenkiste, 2002 ⁷⁶		x
Witzig, 2005 ⁷⁷		x
Wright, 2007 ³³		x

20000161 ⁴⁰		x
20010103 ⁴¹		x

Chapter 6: Discussion

6.1. Discussion of Results

The purpose of this study was to 1) Examine the practice in Newfoundland and Labrador with respect to ESA use in patients with hematologic cancers and 2) To review the current state of the literature around tumor outcome and survival for cancer patients receiving ESAs. A number of organizations, including the Canadian Cancer and Anemia Guidelines Development Group (CCAGDG)¹³, the European Organization for Research and Treatment of Cancer (EORTC)¹⁴ and ASCO and ASH together¹¹ developed guidelines for the use of ESAs in patients with cancer. Despite the existence of these guidelines it has been the experience of the hematologists and medical oncologists in this province that patients with cancer-related anemia are not receiving ESAs.

The first objective of this study was to estimate the number of patients with hematologic cancers in this province that meet ASCO/ASH guidelines for receiving ESAs that actually do and do not receive these medications. A related objective was to determine whether there are demographic factors associated with receipt of an ESA. To accomplish these goals, the charts of patients with diagnoses of multiple myeloma, non-Hodgkin's lymphoma, chronic lymphocytic leukemia and myelodysplasia between 2003 and 2005 were reviewed. For patients with the first three of these diagnoses, only those undergoing chemotherapy are candidates to receive an ESA according to ASCO/ASH guidelines and so only this group was included. All anemic patients with myelodysplasia were eligible.

Of the 110 charts reviewed, the majority of patients had non-Hodgkin's lymphoma; chronic lymphocytic leukemia was the least frequent diagnosis. Despite all of the study patients meeting guideline criteria for receiving an ESA, only 16.4% of them actually did receive one. A number of possibilities may explain this finding: 1) these drugs are quite expensive and coverage provided by the provincial drug program is limited, 2) new literature suggests that there are significant adverse effects for cancer patients treated with ESAs which may have affected physicians' clinical decision making, and 3) other factors, like patient demographics, may have played a role.

ESAs are very costly. For example, for the recommended dose of Eprex of 150 U/kg three times weekly, for a 70 kg person, the weekly cost of Eprex is approximately \$450.00. Medications considered for coverage under the Newfoundland and Labrador Prescription Drug Program (NLPDP) are reviewed by an Expert Advisory Committee (EAC) representing the four Atlantic provinces. In March 2006, the following criteria were put forth by the EAC:

Coverage of Eprex is considered under Special Authorization for:

The treatment of anemia in hematological malignancy in transfusion dependent patients with a baseline Hgb ≤ 90 g/L whose transfusion requirements are ≥ 2 units of packed red blood cells (PRBC/month) over a 3 month period. An initial trial of 12 weeks with documentation of dose, Hgb and therapeutic outcome (# of transfusions) [is required].

Further 12 week cycles can be approved dependent on evidence of clinical response or reduced treatment requirements to < 2 units of PRBC/month. If transfusion requirements increase to ≥ 2 units/month (over a 3 month period), one dose increase may be attempted (maximum dose 60,000 iu per week) ⁷⁸.

Given the high cost of ESAs, many patients are unable to afford these drugs without some form of subsidy. These recommendations, which have been adopted by the NLPDP, clearly prohibit many patients from receiving any government subsidy toward the cost of these drugs. Importantly, they are out of keeping with the numerous national guidelines available. Specifically, the ASCO/ASH guidelines state that ¹¹:

The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level less than or equal to 10 g/dL.

For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentrations below 12 g/dL but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances.

Certainly, these guidelines do not suggest waiting until a person is transfusion dependent or has a hemoglobin concentration of less than 90 g/L. The lack of NLPDP coverage is likely a large, if not the largest, contributing factor to the low ESA use in anemic cancer patients in Newfoundland and Labrador. This is particularly likely to have been the case

between 2003 and 2005, during the time period from which data for this study was collected. During that time, and subsequently, new data has been emerging that highlight important safety concerns around the use of these drugs. This data may have contributed to the low ESA use during the study period to some extent, but is perhaps more likely to play a role in the future.

ESAs improve hemoglobin concentrations or hematocrit levels⁵ and reduce transfusion requirements⁶ in anemic patients with malignancies. There is some evidence that they also improve quality of life⁷. They are, however, known to increase the risk of thromboembolic disease⁸. An even greater potential risk associated with the use of ESAs is tumor progression and decreased survival. The initial clinical evidence for this effect was provided by the BEST⁹ and ENHANCE trials¹⁰. These trials both had some methodological concerns and the majority of patients taking ESAs were not in fact anemic. Given the lack of high quality evidence linking ESAs to poorer disease outcomes at the time, this concern was likely not a major contributor to the low ESA use found in this study.

In addition to the cost of ESAs and emerging concerns about their safety profile, a third possible explanation for the low ESA use found in this study might be the demographic features of the sample. One might speculate, for example, that the age of the patient could be a factor in the decision about whether to start an ESA. There are many potential causes of anemia in older individuals and it may have been felt that etiologies other than cancer-related anemia were a greater contributor to some patients' anemia. Similarly, place of residence might play a role in determining which patients receive ESAs. Given the size of the province and the distance that patients may have to

travel to come to St. John's, it is not uncommon for patients to have their chemotherapy regimen initiated in St. John's and continued in a rural area of the province. It is possible patients seen infrequently by a hematologist or medical oncologist may not have an ESA initiated.

The burden of anemia in this study was represented in three ways: 1) the overall average weekly hemoglobin concentration, 2) the proportion of time spent with a hemoglobin concentration less than 100 g/L and 3) the number of red blood cell transfusions that patients received.

The mean weekly hemoglobin concentration of the patients in this study was 89.1 g/L and the patients' hemoglobin concentrations were under 100 g/L for about 75% of the study weeks. Patients received an average of one red blood cell transfusion every three weeks. These results indicate that these patients were significantly anemic and, by ASCO/ASH 2002 criteria, should have received an ESA. For some patients, individual characteristics may have led to a decision not to use an ESA, for example, a high risk of thromboembolism, however these features would likely have applied to a few patients only. With approximately 84% of patients not receiving an ESA, it is more likely that systemic effects (as discussed above) were responsible.

The effect of two demographic factors on ESA use in patients with hematologic malignancies was examined. No significant difference between the ages of the patients receiving and not receiving an ESA was detected. The average age in the group that received an ESA was 72.9 years versus 70.1 years in the group that did not.

There was significantly more ESA use in patients living in urban areas of the province; 61.1% of patients from urban areas received Eprex versus 38.9% of patients from rural areas. It is possible that patients living in rural areas may not have been prescribed an ESA as a result of having less contact with a hematologist or medical oncologist.

In summary, the results of this study suggest that 16.4% of patients with hematologic malignancies between 2003 and 2005, meeting the 2002 ASCO/ASH criteria for receiving an ESA actually received one. There are several potential reasons for this. It may be that the cost of these medications is prohibitive for many patients given that NLPDP coverage for them is very limited. The data linking them to poor disease control and decreased survival was beginning to emerge during the period from which data were collected. This was unlikely to have played a major role, but may have contributed to an extent to the low ESA use. Demographic factors may have affected ESA use and the results demonstrated that that indeed, more patients from urban areas of the province received one. Finally, individual factors, like thromboembolic risk, may have played a role. These results also indicate that these patients were significantly anemic. Their average weekly hemoglobin was 89.5 g/L and for 75% of the study period, hemoglobin levels were less than 100 g/L. Patients were transfused an average of once every three weeks.

6.2. Effect of Place of Residence on Receipt of an Erythropoiesis-Stimulating Agent

This study found significantly more ESA use in patients living in urban rather than rural areas of the province; 61.1% of patients from urban areas received an ESA versus 38.9% of patients from rural areas. This finding is likely related to the fact that these drugs are not covered under the provincial drug plan for most patients. Another possibility is lesser access to a prescribing hematologist or oncologist.

In general, Canadians living in rural areas are more likely to live in lower socioeconomic conditions, have attained a lower level of education, exhibit less healthy behaviours and to have a higher overall mortality rate than their urban counterparts.⁷⁹ While in Canada, access to universally insured health services remains largely unrelated to income, many low and moderate income Canadians have limited or no access to certain health services and prescription drugs.⁸⁰ While in most provinces in Canada, erythropoiesis-stimulating agents are covered by the provincial drug plan,⁸¹ as described above, the criteria for NLPDP coverage of ESAs in Newfoundland and Labrador is prohibitive for most patients.

6.3. The Future of Erythropoiesis-Stimulating Agents

The clinical benefits associated with the use of ESAs in cancer patients include improved hemoglobin or hematocrit, decreased red blood cell transfusions and possibly,

improved quality of life. There is an increased risk of thromboembolism in patients taking ESAs and questionable decreased survival.

In order to address new evidence surrounding the use of ESAs in cancer-related anemia, ASH and ASCO published a clinical practice guideline update on their use in 2007¹². These updated guidelines continue to recommend an ESA for patients with hemoglobin levels less than 100 g/L/, specifically,

The use of epoetin or darbepoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a Hb concentration that is approaching, or has fallen below, 10 g/dL, to increase Hb and decrease transfusions.

These guidelines address the thromboembolic risk by suggesting that clinicians “carefully weigh the risks of thromboembolism in patients for whom epoetin or darbepoetin are prescribed.” The specific risk factors for thromboembolism in patients taking these medications have not been defined and therefore established, general risk factors for thrombosis should be taken into considered. No studies have yet evaluated the use of aspirin or anticoagulants to modulate the risk of thromboembolism in patients taking ESAs for cancer-related anemia.

The risk of disease progression while taking an ESA appears to be primarily in those patients not receiving concurrent chemotherapy. There is evidence supporting the use of ESAs in patients with myelodysplasia^{36,37}, however, in other hematologic or solid malignancies, they may be associated with an increased risk of death in patients not receiving chemotherapy.

The decision whether to use an ESA in a patient with cancer-related anemia will depend on the benefit-risk ratio for that particular patient. They should be used cautiously in patients with risk factors for thromboembolic disease and should not be used in patients that are not undergoing chemotherapy. The hematologic response should be monitored and the dose titrated to maintain a hemoglobin concentration at or near 120 g/L. In patients in whom there is no hematologic response, the drug should be discontinued after a trial period of six to eight weeks.

6.4. Study Limitations

For the first part of this study a retrospective design was chosen. The benefit of this study design was the fact that practice would not be altered by the study itself. The study did have several limitations, primarily: 1) The design was retrospective and 2) Information about quality of life and safety was not collected. A retrospective design was chosen for its simplicity, low cost, and again so as not to affect practice as the data were being collected. If the reason for low ESA use was physician-driven, then knowledge of the study might change the way that ESAs were prescribed. One of the disadvantages of the retrospective design is the fact that data collection relied on medical records, which may have had errors or omissions. Another drawback of the retrospective design for this study is that conclusions can only be made about ESA use between 2003 and 2005.

Another limitation is that information about quality of life was not collected. This was unfortunately not possible given the study design. It would also be valuable to have

safety information about this group of patients. Again, given the study design it would have been difficult to ascertain whether side effects could be attributed to the ESA.

6.5. Future Directions

Further, high-quality studies are needed to determine more definitively whether ESAs affect quality of life. The specific risk factors for thromboembolic disease in patients treated with ESAs must be elucidated, as does whether aspirin or anticoagulation can modulate the risk. Finally the effect of ESAs on disease progression and survival warrants further study. Given the quality of currently available data, the effect of ESAs, titrated to maintain a hemoglobin concentration near 120 g/L on a population of patients with cancer-related anemia undergoing chemotherapy is still unknown.

6.6. Conclusions

For patients with hematologic malignancies in Newfoundland and Labrador, ESAs are underutilized. In this study sample, only 16.4% of patients meeting the 2002 ASCO/ASH guidelines for the use of ESAs in cancer patients received one. The patients were quite anemic with an average hemoglobin of 89.1 g/L. Hemoglobin concentrations were under 100 g/L for 75.3% of the study period and patients received an average of one red blood cell transfusion every three weeks. Patients living in urban areas of the province received an ESA more often than patients in rural areas.

ESAs are an important part of supportive cancer care. They improve hemoglobin concentrations, decrease transfusion requirements and likely benefit quality of life. The factors contributing to the low use of ESAs in this province should be further elucidated and measures should be taken to improve their use to meet national and international standards of care. Patient selection is important as ESAs increase the risk of thromboembolism. There is evidence that ESAs may be harmful in cancer patients not undergoing chemotherapy and they should not be used in this group.

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Appendix A

Summary of ASCO/ASH Guidelines on the Use of Epoetin in Cancer Patients

1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level less than or equal to 10 g/dL. Red blood cell transfusion is also an option depending upon the severity of anemia or clinical circumstances.
2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration below 12 g/dL but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. Red blood cell transfusion is also a therapeutic option when warranted by severe clinical conditions.
3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4-8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40 000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice-weekly regimens.
4. Continuing epoetin treatment beyond 6-8 weeks in the absence of response (eg, less than 1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been

attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.

5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.

6. Baseline and periodic monitoring of iron, total iron-binding capacity (TIBC), transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.

7. There is evidence from one well-designed, placebo-controlled randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.

8. Physicians caring for patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed following chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.

Appendix B



Memorial

University of Newfoundland

Office of Research and Graduate Studies (Medicine)
Faculty of Medicine
The Health Sciences Centre

May 11, 2006

Reference #06.41

Dr. Dawn Sheppard
C/o Dr. Kuljit Grewal
Hematology
Faculty of Medicine
Health Sciences Centre

Dear Dr. Sheppard:

This will acknowledge the revised application and consent form which you provided for your research study entitled "**Use of erythropoietin in patients with cancer in Newfoundland and Labrador**".

At the meeting held on **February 16, 2006**, the initial review date of this study, the Human Investigation Committee (HIC) agreed that the revised application and revised consent form could be reviewed by the Co-Chairs and, if found acceptable, full approval of the study be granted.

The Co-Chairs of the HIC reviewed your correspondence, approved the revised application and consent form and, under the direction of the Committee, granted **full approval** of your research study. This will be reported to the full Human Investigation Committee, for their information at the meeting scheduled for **May 25, 2006**.

Full approval has been granted for one year. You will be contacted to complete the annual form update approximately 8 weeks before the approval will lapse on **February 16, 2007**. It is your responsibility to ensure that the renewal form is forwarded to the HIC office not less than 30 days prior to the renewal date for review and approval to continue the study. The annual renewal form can be downloaded from the HIC website

<http://www.med.mun.ca/hic/downloads/Annual%20Update%20Form.doc>.

Modifications of the protocol/consent are not permitted without prior approval from the Human Investigation Committee. Implementing changes in the protocol/consent without HIC approval may result in the approval of your research

St. John's, NL, Canada A1B 3X6 • Tel.: (709) 777-6762 • Fax: (709) 777-7501 • email: rgs@mun.ca

study being revoked, necessitating cessation of all related research activity. Request for modification to the protocol/consent must be outlined on an amendment form (available on the HIC website) and submitted to the HIC for review.

For a hospital-based study, it is your responsibility to seek the necessary approval from the Health Care Corporation of St. John's and/or other hospital boards as appropriate.

This Research Ethics Board (the HIC) has reviewed and approved the application and consent form for the study which is to be conducted by you as the qualified investigator named above at the specified study site. This approval and the views of this Research Ethics Board have been documented in writing. In addition, please be advised that the Human Investigation Committee currently operates according to the Tri-Council Policy Statement and applicable laws and regulations.

Notwithstanding the approval of the HIC, the primary responsibility for the ethical conduct of the investigation remains with you.

We wish you every success with your study.

Sincerely,



John D. Harnett, MD, FRCPC
Co-Chair
Human Investigation Committee

Richard S. Neuman, PhD
Co-Chair
Human Investigation Committee

JDH;RSN\jd

C Dr. C. Loomis, Vice-President (Research), MUN
Mr. W. Miller, Director of Planning & Research, HCCSJ

Appendix C



St. Clare's Mercy Hospital
154 LeMarchant Road
St. John's, NL
Canada A1C 5B8
T: (709) 777-5000
F: (709) 777-5210
www.easternhealth.ca

June 14, 2006

Ms. Dawn Sheppard
Resident
C/o Dr. K. Grewal
Hematology Oncology
HSC

Dear Ms. Sheppard:

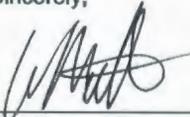
Your research proposal "*HIC # 06. 041 – Use of erythropoietin in patients with cancer in Newfoundland*" was reviewed by the Research Proposals Approvals Committee (RPAC) of the Health Care Corporation of St. John's at its meeting on June 13, 2006 and we are pleased to inform you that the proposal has been approved.

The approval of this project is subject to the following conditions:

- The project is conducted as outlined in the HIC approved protocol;
- Adequate funding is secured to support the project;
- In the case of Health Records, efforts will be made to accommodate requests based upon available resources. If you require access to records that cannot be accommodated, then additional fees may be levied to cover the cost;
- A progress report being provided upon request.

If you have any questions or comments, please contact Lynn Purchase, Manager of the Patient Research Centre at 777-7283.

Sincerely,



Mr. Wayne Miller
Senior Director, Corporate Strategy & Research
Chair, RPAC

cc: Ms. Lynn Purchase, Manager, Patient Research Centre
Ms. Louanne Kinsella, Program Director Medicine
Dr. H. Edstrom, Clinical Chief Medicine

Appendix A

Summary of ASCO/ASH Guidelines on the Use of Epoetin in Cancer Patients

1. The use of epoetin is recommended as a treatment option for patients with chemotherapy-associated anemia and a hemoglobin concentration that has declined to a level less than or equal to 10 g/dL. Red blood cell transfusion is also an option depending upon the severity of anemia or clinical circumstances.
2. For patients with declining hemoglobin levels but less severe anemia (those with hemoglobin concentration below 12 g/dL but who have never fallen below 10 g/dL), the decision of whether to use epoetin immediately or to wait until hemoglobin levels fall closer to 10 g/dL should be determined by clinical circumstances. Red blood cell transfusion is also a therapeutic option when warranted by severe clinical conditions.
3. The recommendations are based on evidence from trials in which epoetin was administered subcutaneously thrice weekly. The recommended starting dose is 150 U/kg thrice weekly for a minimum of 4 weeks, with consideration given for dose escalation to 300 U/kg thrice weekly for an additional 4-8 weeks in those who do not respond to the initial dose. Although supported by less strong evidence, an alternative weekly dosing regimen (40 000 U/wk), based on common clinical practice, can be considered. Dose escalation of weekly regimens should be under similar circumstances to thrice-weekly regimens.
4. Continuing epoetin treatment beyond 6-8 weeks in the absence of response (eg, less than 1-2 g/dL rise in hemoglobin), assuming appropriate dose increase has been

attempted in nonresponders, does not appear to be beneficial. Patients who do not respond should be investigated for underlying tumor progression or iron deficiency. As with other failed individual therapeutic trials, consideration should be given to discontinuing the medication.

5. Hemoglobin levels can be raised to (or near) a concentration of 12 g/dL, at which time the dosage of epoetin should be titrated to maintain that level or restarted when the level falls to near 10 g/dL. Insufficient evidence to date supports the "normalization" of hemoglobin levels to above 12 g/dL.

6. Baseline and periodic monitoring of iron, total iron-binding capacity (TIBC), transferrin saturation, or ferritin levels and instituting iron repletion when indicated may be valuable in limiting the need for epoetin, maximizing symptomatic improvement for patients, and determining the reason for failure to respond adequately to epoetin. There is inadequate evidence to specify the optimal timing, periodicity, or testing regimen for such monitoring.

7. There is evidence from one well-designed, placebo-controlled randomized trial that supports the use of epoetin in patients with anemia associated with low-risk myelodysplasia, but there are no published high-quality studies to support its use in anemic myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia patients in the absence of chemotherapy. Treatment with epoetin for myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia patients experiencing chemotherapy-associated anemia should follow the recommendations outlined above.

8. Physicians caring for patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia are advised to begin treatment with chemotherapy and/or corticosteroids and observe the hematologic outcomes achieved solely through tumor reduction before considering epoetin. If a rise in hemoglobin is not observed following chemotherapy, epoetin should be used in accordance with the criteria outlined above for chemotherapy-associated anemia if clinically indicated. Blood transfusion is also a therapeutic option.

Appendix B



Memorial

University of Newfoundland

Office of Research and Graduate Studies (Medicine)
Faculty of Medicine
The Health Sciences Centre

May 11, 2006

Reference #06.41

Dr. Dawn Sheppard
C/o Dr. Kuljit Grewal
Hematology
Faculty of Medicine
Health Sciences Centre

Dear Dr. Sheppard:

This will acknowledge the revised application and consent form which you provided for your research study entitled "Use of erythropoietin in patients with cancer in Newfoundland and Labrador".

At the meeting held on **February 16, 2006**, the initial review date of this study, the Human Investigation Committee (HIC) agreed that the revised application and revised consent form could be reviewed by the Co-Chairs and, if found acceptable, full approval of the study be granted.

The Co-Chairs of the HIC reviewed your correspondence, approved the revised application and consent form and, under the direction of the Committee, granted **full approval** of your research study. This will be reported to the full Human Investigation Committee, for their information at the meeting scheduled for **May 25, 2006**.

Full approval has been granted for one year. You will be contacted to complete the annual form update approximately 8 weeks before the approval will lapse on **February 16, 2007**. It is your responsibility to ensure that the renewal form is forwarded to the HIC office not less than 30 days prior to the renewal date for review and approval to continue the study. The annual renewal form can be downloaded from the HIC website

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Dr. D. Sheppard
Reference # 06.41
May 11, 2006

Page 2

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We wish you every success with your study.

Sincerely,



John D. Harnett, MD, FRCPC
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June 14, 2006

Ms. Dawn Sheppard
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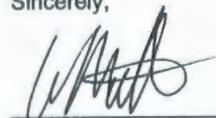
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Mr. Wayne Miller
Senior Director, Corporate Strategy & Research
Chair, RPAC

cc: Ms. Lynn Purchase, Manager, Patient Research Centre
Ms. Louanne Kinsella, Program Director Medicine
Dr. H. Edstrom, Clinical Chief Medicine

